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Implantation of a Vascular Access Button for Chronic Blood Sampling and Drug Administration in the Rabbit

Jon Ehrmann *, Wendy Johnson, Arlene de Castro and Marcie Donnelly

Bristol Myers Squibb, P.O. Box 4000, Princeton, NJ 08540, USA
* Correspondence: jon.ehrmann@bms.com; Tel.: +1-609-252-3684

Abstract: Rabbits are commonly used for pharmacokinetic (PK) and toxicokinetic (TK) studies in the research setting, requiring repetitive venipuncture, which can be challenging in this species. The auricular vessels are commonly used for venipuncture in rabbits. The repetitive access of these delicate vessels can lead to trauma such as hematomas causing venipuncture to become more challenging as the study progresses. In turn, this leads to missed time points or insufficient blood samples. Surgical models for chronic vascular access in rabbits are common throughout the industry. Common models include exteriorized vascular catheters and implanted vascular access ports. However, these implants come with their own complications and restrictions when used in rabbits. Therefore, the authors evaluated the use of a vascular access button (VAB), an implant commonly used in small rodents, as a refinement to the current chronic models in use in the industry. Seventeen rabbits were implanted with either single or dual channel VABs. The catheters were implanted in the femoral artery and/or vein and then tunneled subcutaneously to the button on the dorsal thoracic area. Overall, the results were outstanding, and an established model was created. The average patency rate was 316 days with several implants still patent after 2 years. The authors feel the implantation and use of a vascular access button in rabbits for routine PK studies is an excellent refinement. The rabbits tolerate the buttons extremely well with minimal issues. The patency rate is equal to or better than vascular access ports and when used with the tethering system, provides a hands-off method for blood collection and intravenous administration in rabbits during PK studies.

Keywords: rabbit; blood collection; chronic; vascular access; vascular access button

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1. Introduction

Rabbits are commonly used for pharmacokinetic (PK) and toxicokinetic (TK) studies in the research setting. These types of studies require the administration of a compound followed by a process of tracking the absorption of the compound via the collection of blood samples during a set number of time points. Common sites for venipuncture in the rabbit include the jugular, cephalic, lateral saphenous, and auricular veins. The auricular veins and/or arteries were the most frequently used vessels in conscious rabbits for PK studies [1–3]. However, the combination of required repetitive venipuncture and the delicate nature of the auricular vessels causes blood collection to become increasingly challenging as a typical PK study progresses. Additionally, this process can be very stressful to the rabbits especially as the ears become bruised and sensitive due to the repetitive venipuncture. Additionally, venipuncture in conscious rabbits requires the use of physical restraint and/or the use of a restraint device to perform these procedures. Rabbits are a challenging species to acclimate to these types of procedures and even well-acclimated rabbits will twitch the ear slightly during venipuncture, disrupting the sample collection and quite often resulting in a small hematoma. The combination of all the factors discussed above result in limited opportunities for blood sampling as a study progresses. This could cause missed time points or insufficient blood volumes at the time of sampling.

Animal models for chronic vascular access in rabbits are common throughout the industry. Common models include exteriorized vascular catheters and implanted vascular access ports. An exteriorized vascular catheter is simply a catheter surgically implanted in a vessel, such as the femoral or jugular vein, which is then exteriorized somewhere on the body, usually between the shoulder blades. Exteriorized vascular catheters have several drawbacks such as sepsis due to the catheter exiting the skin, single housing, the need for a protective jacket, and shortened patency [1]. Vascular access ports are implanted devices that consist of a catheter implanted in a vessel and then connected to a subcutaneously placed dome under the skin [4,5]. The dome can be accessed repeatedly via a special needle. Our experience with vascular access ports in rabbits shows that, although the ports have the potential to work well, they come with significantly more complications when compared with vascular access buttons which are discussed later in this document.

To refine the process and be consistent with our commitment to the 3Rs, we implanted seventeen rabbits with vascular access buttons to evaluate the model as a potential refinement to exteriorized catheters and vascular access ports. A vascular access button is a device that consists of a catheter implanted in a vessel and connected to a hub that is exteriorized, usually on the dorsal thoracic area. The hub has pin ports that can be repeatedly accessed via a special adapter. The hub is protected by a magnetic cap. The goals were to reduce the stress encountered by rabbits while on study and to provide a reliable model for repetitive blood collection and intravenous infusion of compounds.

2. Materials and Methods

2.1. Animals

All animals were maintained in accordance with the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act regulations. Seventeen specific-pathogen-free, female/male New Zealand white rabbits (Envigo) at 10–12 months of age, with an average weight of 3 kg were used in the study. Each rabbit was singly housed upon receipt in stainless steel pens in an AAALAC accredited facility with controlled environmental parameters including a room temperature set point of 66 °F with a range of 62–70 °F, relative humidity set point of 50% with a range of 30–70%, light cycle 12 h light/12 h dark). The animals were fed a certified diet once a day (Lab Diet 5325 Hi-Fiber Rabbit), provided daily edible enrichment and hay (Timothy Hay Mini Bales certified, Bioserv), and water ad libitum. The rabbits were also provided with enrichment toys and play activity daily. All procedures described within this manuscript were approved by the site governing Institutional Animal Care and Use Committee.

2.2. Implant

The vascular access button (Instech Labs, Plymouth Meeting, PA, USA) consists of an exteriorized portion which is a magnetized plastic hub with pin ports. The pin ports act as valves, allowing bidirectional flow when accessed with the specialized adapter. Below the hub is a mesh which will promote tissue ingrowth once implanted subcutaneously. On the underside of the implant are titanium pins, which is where the vascular catheters are attached. The implant can be ordered with as many pin ports as you would like, in our case, we used two, one for arterial access and the other for venous. The vascular catheters were 3.0 French polyurethane with permanent beads placed at 17 cm from the tip of the catheter. Additionally, the catheter tip was rounded to prevent vessel trauma and decrease fibrin from collecting around it (Figure 1).

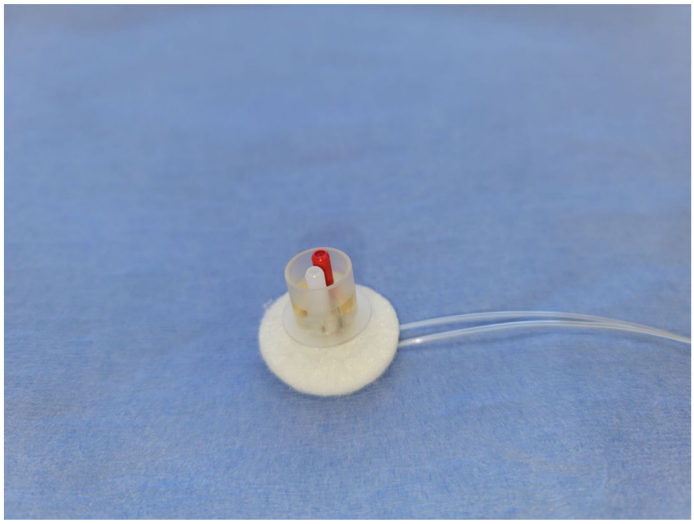

Figure 1. Vascular access button implant. The red and white pins are color-coded for vessel type, red is for arterial and white for venous.

2.3. Pre-Operative Preparation

Physical examinations and baseline complete blood counts and biochemical profiles were conducted within four weeks of surgery. The day before the surgery, a non-steroidal anti-inflammatory drug (NSAID), meloxicam (Covetrus, Dublin, OH, USA), was administered orally at 1 mg/kg. The morning of surgery, a basic pre-surgical examination was performed to ensure the animal was healthy and to provide baseline values for intra-operative and post-operative monitoring. The animals were pre-medicated with glycopyrrolate (West-Ward, Eatontown, NJ, USA), 0.01 mg/kg, ketamine (Vedco, St. Joseph, MO, USA) 35 mg/kg and xylazine (Akorn, Lake Forest, IL, USA) 5 mg/kg intramuscularly. Once the appropriate level of sedation was achieved, the rabbit was intubated with a 3.0 mm cuffed endotracheal tube utilizing a rigid endoscope-guided technique. An intravenous (IV) catheter was placed in an auricular vein and a balanced electrolyte solution was administered at 6 mL/kg/hr. General anesthesia was maintained with isoflurane (Vedco, St. Joseph, MO, USA) via oxygen throughout the procedure. Eye lubricant (Altaire Pharmaceuticals, Aquebogue, NY, USA) was applied to both eyes. A pre-operative antibiotic, cefazolin (West-Ward, Eatontown, NJ, USA) at 20 mg/kg, was slowly administered intravenously. After the animal was at the proper level of anesthesia, the surgical field was prepared. This involved clipping the hair from the right inguinal area extending up to the dorsal back including the scapula and neck. The clipped area was wiped with a diluted chlorhexidine solution (Butler Schein, Dublin, OH, USA).

2.4. Surgical Procedure

The animal was transported to the surgical suite and the surgical area was aseptically prepared using a 5 min chlorohexidine surgical scrub (Fort Dodge, Fort Dodge, IA, USA), a 70% isopropyl alcohol rinse, and an application of a final prep solution, DuraPrep™ (3M, St. Paul, MN, USA). The proposed surgical incision sites were aseptically draped via a four-corner draping technique and an adhesive barrier (Ioban™, 3M, St. Paul, MN, USA). After the animal was at the proper level of anesthesia, a 4 cm skin incision was made in the inguinal area. Blunt and sharp dissection was used to isolate the femoral artery and/or vein. Three ligatures were placed around each vessel for proper exposure. The catheter length was predetermined with permanent suture beads placed 17 cm from the tip of the catheter ensuring the tip of the catheter(s) will lie distal to the level of the renal artery and/or vein. In the inguinal incision, the artery was ligated with the distal suture, 3-0 Prolene (Ethicon, San Lorenzo, Puerto Rico), and the proximal ligatures, 3-0 Vicryl (Ethicon, Guaynabo, Puerto Rico), were used to both elevate the vessel and temporarily

occlude blood flow (Figure 2). A 1 mm transverse incision was made on the vessel with an iris scissor and a catheter introducer was positioned in the lumen to aid in the placement of the catheter. The catheter was advanced into the vessel until the permanent bead was in line with the distal ligature. The catheter was secured in place with the two proximal ligatures ensuring both the vessel and catheter were tightened together. It is important to tie these ligatures tight enough to prevent catheter migration, but not so tight as to cause occlusion of the catheter. The distal suture was secured between the two beads anchoring it in place. The same process was repeated for catheterization of the femoral vein for the animals with dual channel implants. The catheter(s) were then tunneled subcutaneously to a small stab incision on the flank and then tunneled again to a 4 cm incision just caudal to the shoulder blades (original procedure) or to the middle of the dorsal thoracic area (refined procedure). A circular incision was created on the neck/back for the exteriorized portion of the button via an 8 mm biopsy punch (Medline, Northfield, IL, USA). This circular incision was made a few inches away from the incision where the catheters exited so the incision line would not lay against the button and interfere with healing (Figure 3). The catheter was cut to length and secured to the button with 3-0 Nylon (Ethicon, San Lorenzo, Puerto Rico). The button was passed under the skin, so the access hub came out through the circular incision created by the biopsy punch. The button has a layer of Dacron mesh adhered to the bottom of the hub which promotes rapid tissue ingrowth; thus, the button does not require tacking to the underlying musculature. After placement of the vascular button, each catheter was flushed with normal saline solution and the locking solution, taurolidine catheter solution (TCS) (Access Technologies, Skokie, IL, USA) was instilled to prevent thrombus formation within the catheter lumen.

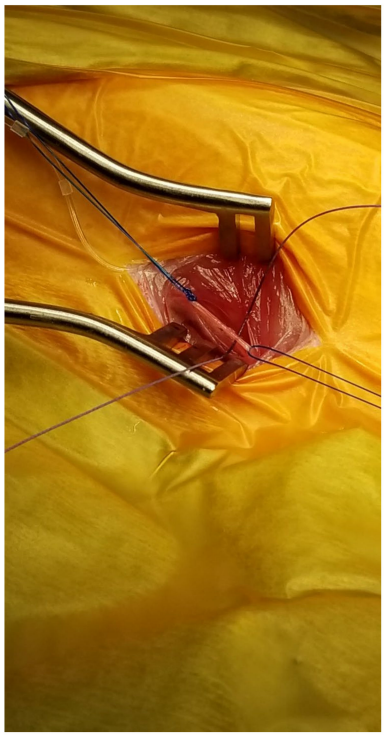

Figure 2. Isolation of femoral artery for catheterization.

Both skin incisions were closed in a similar fashion. The subcutaneous tissue was closed with a monofilament absorbable suture material, 3-0 PDS (Ethicon, Guaynabo, Puerto Rico), in a simple continuous pattern. The subcuticular layer was closed using a monofilament absorbable suture material, 4-0 PDS (Ethicon, Guaynabo, Puerto Rico), in an inverted interrupted pattern. A local block, 0.25% bupivacaine (Hospira, Lake Forest, IL,

USA), was administered to each incision during closure. A protective magnetic cap was placed over the implant at the end of the procedure (Figure 4).

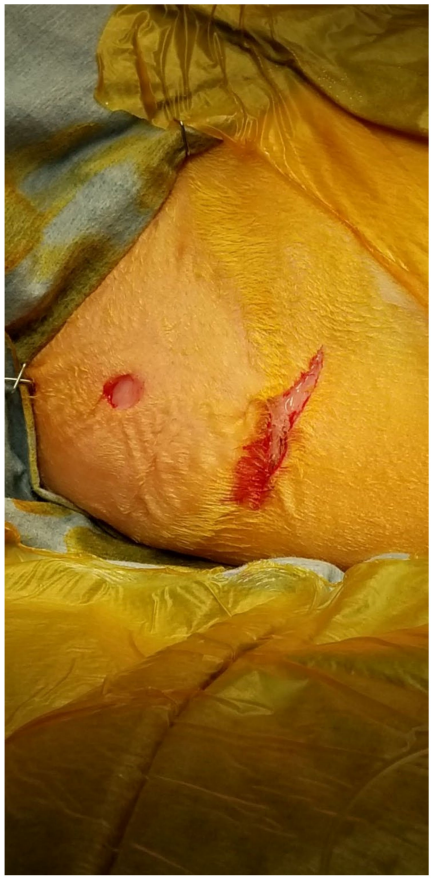

Figure 3. Circular incision created by a biopsy punch for button placement.

Figure 4. Vascular access button with protective magnetic cap.

2.5. Post-Operative Care

Routine post-operative care was followed focusing on thermoregulation, intravenous fluid administration, analgesia, pain assessment, and documentation of physiological parameters every 30–60 min. Immediately following surgery, the rabbit was moved to a heated recovery cage and administered meloxicam (Covetrus, Dublin, OH, USA), 1 mg/kg SQ. Intravenous fluids were discontinued once the rabbit was sternal and moving about the cage. An intramuscular dose of buprenorphine (Reckitt Benckiser Healthcare, North Chesterfield, VA, USA) at 0.03 mg/kg was administered at the end of the day. Meloxicam (Covetrus, Dublin, OH, USA) 1 mg/kg SQ was continued for three post-operative days. Each rabbit was evaluated daily for incisional healing, appetite, fecal and urine output, signs of pain or distress, and activity level. All animals healed within ten to fourteen days of the procedure.

2.6. Catheter Maintenance

The hair surrounding the implant was matted down using sterile water or 70% isopropyl alcohol. The protective magnetic cap was removed. Following aseptic technique, the buttons were prepped prior to access by wiping the pin ports and the outside of the button with 70% isopropyl alcohol followed by a ChloraPrep™ (Care Fusion, El Paso, TX, USA) swab. The solution was allowed to dry for ~2 min. All the materials used to access the button were sterile and handled in an aseptic manner with sterile gloves. Each channel (arterial and venous) was accessed, confirmed patent via the ability to aspirate blood, flushed with ~3 mL of sterile saline, and locked with taurolidine catheter solution (TCS) (Access Technologies, Skokie, IL, USA). The prep solution was then removed by wiping the exterior of the implant with 70% isopropyl alcohol. The protective cap was also cleaned with alcohol and allowed to dry prior to being placed back on the implant. The initial patency check occurred at one-week post-op and then routine maintenance continued at monthly intervals.

3. Results

3.1. Patency

At the time of this publication, seventeen rabbits have been implanted with vascular access buttons. The authors define patency as the ability to aspirate blood. Six of those implants were arterial only and the other eleven had both arterial and venous channels. The first cohort, the six arterial-only VABs, were instrumented in June 2019 and remained patent for the length of their study use, which was 250 days at which time they were humanely euthanized for study needs. One of those six, lost bidirectional patency at 112 days allowing for flushing in but no blood aspiration. Therefore, 83% of the cohort maintained patency for the length of the study. The second cohort of four rabbits were instrumented with dual channel VABs in May of 2021. All the venous channels are currently patent, two of the arterial channels lost patency shortly after surgery, which is discussed in the next section, one lost patency during a study (329 days), and the other is currently patent. Therefore, 75% of the cohort has maintained venous patency for over 600 days. The third cohort of four rabbits were instrumented with dual channel VABs in February 2022. Two of those currently have dual patency and the other two died approximately one month after surgery due to unrelated GI complications. The two remaining rabbits from this cohort have maintained dual patency for over 300 days. The final cohort of three rabbits were instrumented with dual channel VABs in June 2022. All three have maintained dual patency for over 195 days. Please refer to Table 1 for additional details.

Table 1. Patency in days for rabbits with vascular access buttons. "+" symbol denotes the animals are currently in the colony.

Animal ID	Age (Months)	Weight (Kg)	Model	Surgical Outcome	Patency (Days)	Comments
1	14	4	Arterial	Successful	253	
2	12	3.8	Arterial	Successful	250	
3	15	3.9	Arterial	Successful	253	
4	14	4.5	Arterial	Successful	252	
5	14	4.1	Arterial	Successful	112	
6	14	4.6	Arterial	Successful	251	
7	6	3.4	Arterial and venous	Successful, arterial catheter only advanced 8 cm	617+	Arterial catheter is infusion only
8	6	3.3	Arterial and venous	Successful, arterial catheter only advanced 10 cm	616+	Arterial catheter is infusion only
9	6	3.4	Arterial and venous	Successful	608+	
10	6	3.4	Arterial and venous	Successful	329	
11	14	3.8	Arterial and venous	Successful	322+	
12	9	4	Arterial and venous	Successful	314+	
13	12	3.4	Arterial and venous	Successful	59	Removed from the colony at day 59
14	12	4	Arterial and venous	Successful	76	Removed from the colony at day 76
15	16	3.8	Arterial and venous	Successful	196+	
16	16	3.6	Arterial and venous	Successful	195+	
17	16	3.5	Arterial and venous	Successful	182+	

3.2. Surgical Complications

As noted in the patency section, two rabbits lost patency to the arterial channels shortly after surgery. During the catheterization portion of the surgery for these two rabbits, the authors were not able to advance the catheter completely into the artery. In each of the rabbits, the arterial catheter was advanced approximately 10 cm at which point significant resistance was encountered while attempting to advance the catheter the remaining 7 cm. This complication was not encountered in the first cohort of rabbits. Since this was a new issue and the catheters had good patency during the surgery, it was decided to leave them as is and trim the extra catheter off prior to connecting it to the button. However, the catheters were not patent at the one-week post-op flush. The catheter was easy to flush but did not give blood back and remained this way for the life of the implant. The authors hypothesize the catheter tips were laying in the iliac or iliac-aortic bifurcation instead of the abdominal aorta and the area is too small to allow for blood draw and thus the unidirectional patency. This hypothesis will be confirmed via necropsy when the animals are removed from the colony. This complication, which the authors assume was vasoconstriction and/or spasm induced by the introduction of the catheter, has been encountered several times since these two rabbits. The complication can be remedied by holding the catheter very close to the

insertion point and advancing a few millimeters of the catheter at a time until the entire catheter has been inserted.

3.3. Post-Operative Complications

Surgery was successful in each case and all seventeen rabbits recovered well with minimal post-operative complications. The few complications encountered included one rabbit chewing at the inguinal incision and another removing the protective cap and chewing at the implant. A rabbit chewing on or near the inguinal incision is not uncommon. The authors assume this is due to the hydrolysis of suture material creating a pruritic response. An Elizabethan collar was placed on the rabbit to prevent further trauma and an antibiotic ointment was applied topically. The wound resolved within seven days of treatment.

The second complication was rather unique and only seen in one rabbit thus far. The rabbit was consistently removing the protective cap. Although never witnessed, the authors assume the rabbit was accomplishing this by scratching at it or grabbing it with his teeth. One of these incidences occurred overnight and resulted in the rabbit chewing at the pin ports of the VAB to the point where they could no longer be accessed. Therefore, a surgery to replace the damaged button was performed in which the old button was dissected out of the implantation pocket, a new button was attached to the existing catheters and placed back into the original pocket. Although there was significant tissue growth over the felt on the bottom of the original implant, it was a straightforward procedure to bluntly dissect the tissue away and remove the implant. The replacement VAB was implanted in the same manner as described in the surgical procedure above. The new implant healed uneventfully.

An additional complication seen in a few animals was difficulty removing the protective cap during the post-operative period. An exudate from the incision site weeps up into the cap. Since this substance is extremely sticky it can make removing the cap quite challenging at times. The authors found a persistent pull-and-twist method will finally dislodge the cap from the adherence. The cap and button were then cleaned with alcohol prior to placing the cap back on. As a preventative measure, the cap was removed and cleaned once a day during the first 7–10 days of healing. This additional step has prevented further adherence of the magnetic caps during healing.

4. Discussion

The implantation and use of vascular access buttons in rabbits for routine PK studies has been an excellent refinement for our department. The rabbits tolerate the buttons extremely well with minimal issues. Once the implant has healed, there has been no migration or necrosis noted, nor do we see continuous exudate commonly seen with other exteriorized implants. Occasionally, we find a protective cap missing from the implant, usually laying in the bottom of the rabbit's cage and we simply clean it and replace it.

Sepsis can be a common issue with exteriorized implants since there is opportunity for bacteria to enter via the skin. As mentioned earlier in the manuscript, this is a significant drawback to exteriorized catheters. To date, there have been no incidences of sepsis or bacterial infection of the implant in our rabbits. The use of aseptic technique is a must when accessing the implant to prevent the introduction of bacteria. The lack of sepsis in the vascular access button further supports its use as a refinement for chronic vascular access in rabbits.

The protective caps also create an opportunity for social housing of the animals. The rabbits discussed in this manuscript were received from the vendor as singles and thus we did not attempt to create social pairs. In the future, we plan to bring rabbits in from the vendor as established pairs and thus will maintain this status even with VAB implants. We currently social house rats with VABs at our facility with no issues.

4.1. Pharmacokinetic Studies

The VABs have provided a stress-free environment for both the rabbit and technician regarding running a PK study. The rabbits are acclimated to a stainless-steel restraint

device several weeks prior to the first study. Once acclimated, the rabbits are placed in the device with room to move forward and backward but preventing them from turning around or jumping out of it. The VAB is then aseptically prepped as discussed previously and then accessed using a magnetic tethering device (Instech, Plymouth Meeting, PA, USA) (Figure 5). The tethering device allows access to both the arterial and venous channel throughout the length of the study without manipulating the rabbit. Once the VAB is accessed, the tethering device is kept clean by placing it on a sterile drape laying on the restraint device or a nearby table. The lines within the tethering device have a pin port on the ends, identical to the ports on the buttons themselves. They are accessed via a pin port adapter to collect blood or infuse compounds. Once a compound is infused or a blood sample is collected, the lines are flushed with sterile saline and locked with TCS. If time points are close in time to each other, defined as less than one hour, the lines are flushed with saline spiked with 50 units of heparin in 0.9% saline. This avoids the use of too much anticoagulant and does not affect patency due to the frequent sampling and flushing. Once the study is completed for the day, the tethering device is removed and the VAB is flushed directly with sterile saline and locked with the appropriate amount of TCS. It is important to utilize a positive-pressure technique when locking the buttons, otherwise a small amount of blood will be pulled back into the catheter as you disconnect from the pin port. The rabbits have been extremely calm while on study since there is basically no restraint. Additionally, if the study allows for it, the rabbits are given food treats throughout the study.

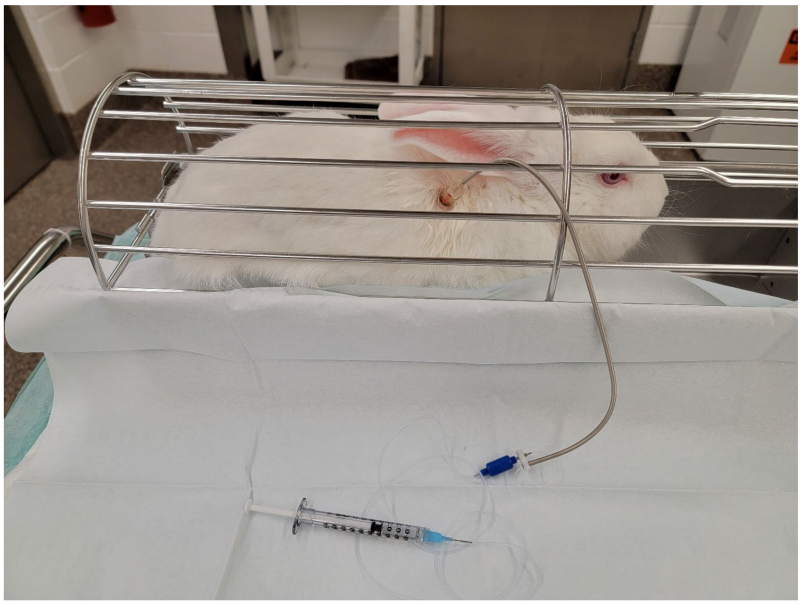

Figure 5. Use of a VAB and magnetic tether during a PK study.

4.2. Refinements

The team has developed several refinements as we gain more experience with the surgical procedure and use of the buttons. One major refinement was to move away from subcutaneously implanted vascular access ports and use buttons exclusively. Prior to buttons, we implanted several rabbits with vascular access ports (VAPs). The initial surgery was successful, however the long-term healing and patency of the VAPs was not ideal. The most significant issue was migration of the port and flipping of the port under the skin. Rabbits do not encapsulate the port as other species, so over time the suture material breaks down and the ports start to migrate or flip. This movement creates tension on the implanted catheter, causing the catheter to back out of the vessel completely or to an area in the vessel where patency was lost. Quite often, the catheter was found wrapped around the port in the subcutaneous pocket during surgical repair procedures. Additionally, the

dermis over the port would become fibrous and thus difficult to access with a Huber needle, often becoming a sensitive procedure for the rabbit.

The authors also identified rabbits to be sensitive to poliglecaprone 25 suture material. In a previous study, fourteen rabbits were instrumented with VAPs, and the surgical incisions were closed with poliglecaprone 25 for both the subcutaneous and subcuticular layers. Although the incision lines healed well, all the animals began chewing the skin near the flank incisions at post-op days 10–14. The authors hypothesize this was from hydrolysis of the suture material creating a significant pruritic response in the rabbit. Since then, we switched to polydioxanone with minimal adverse reactions noted.

The third refinement to discuss is the location of the vascular access button on the rabbit's body. Originally, the VAB was located on the cranial portion of the neck, under the ears. This location was selected as the most viable location where the rabbit could not reach and disturb the button. However, this location had a few drawbacks. First, the rabbit's ears had to be manually held forward to aseptically prep and access the button. Secondly, the button was difficult to access while the rabbit was in a restraint device for study. Therefore, the button was moved to approximately the middle of the back and sits just to the side of the vertebral column. Overall, the rabbits have tolerated the new location quite well with the one exception discussed above. The button at this location on the back is very easy to access, both during manual restraint and within the restraint device. Additionally, the rabbits are calmer since the ears do not have to be manipulated.

The final refinement to mention is the use of a protective cap with a small screw in the side to secure it to the button. The vendor provided this as a solution to the one rabbit constantly removing the magnetic protective cap. The cap covers the button in the same manner as the magnetic version but has a small screw on the side. The screw is tightened by a small Allen wrench securing it to the button. Thus far, the rabbit has not been able to remove the protective cap.

5. Conclusions

The use of a vascular access button in rabbits has proven to be an excellent chronic model for both the administration of intravenous compounds and the collection of serial blood samples. The rabbits tolerate the buttons extremely well with minimal issues. Once the implant has healed, no migration or necrosis has been noted nor is there a continuous exudate commonly seen with other exteriorized implants. Since the button is externalized, it provides a very efficient and low-stress method for both the rabbit and the technician conducting the study. Additionally, the button has proven to be a refinement compared to vascular access ports. The improvements achieved using the button significantly outweigh the post-operative complications encountered with a port, while the patency rate is equal to or better than a port.

Author Contributions: Conceptualization J.E.; methodology, J.E. and W.J.; data curation, J.E., W.J., A.d.C. and M.D.; resources, W.J., A.d.C. and M.D.; writing—original draft preparation, J.E.; writing—review and editing, J.E., W.J., A.d.C. and M.D.; All authors have read and agreed to the published version of the manuscript.

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